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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,402	06/30/2006	Yoram Groner	2488.017	8368

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,402	GRONER ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 9/6/07 have been fully considered but they are not persuasive. Claims 1-9, 13 are pending and under consideration. The amendment has been entered. Claims 10-12, 14-48 are canceled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 13 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-9 are directed to a method of treating a T-cell mediated inflammation disorder in a subject having low activity or no activity of runt-related transcription 3 factor (RUNX3) gene product, the method comprising delivering an active agent, wherein the active agent comprises a polynucleotide encoding RUNX3, that induces expression or over-expression of RUNX3 to the immune cells of said subject, thereby inhibiting the proliferation of T-cells. Embodiments limit the immune cells to thymocytes and dendritic cells (DC). Embodiments limit the active agent, to a polynucleotide encoding RUNX3 and further limitations, wherein the del9very step is performed ex vivo. Claim 13 is directed to a method of attenuating dendritic cell (DC) maturation in a subject having low activity or no activity of RUNX3 transcription factor gene product, the method comprising delivering an active agent, wherein the active agent comprises

a polynucleotide encoding RUNX3, that induces expression or over-expression of RUNX3 to the dendritic cells of said subject, thereby attenuating the dendritic cells maturation in said subject.

The specification discusses that the invention provides methods for treating T cell-related inflammatory conditions and testing agents for effectiveness in treating and/or preventing chronic inflammatory diseases (specification p 1, lines 5-9). The specification teaches that RUNX3 knock out mice develop a perturbed distribution of CD4+/CD8+ T lymphocytes (example 1), increased levels of IL-5 (example 2) and spontaneous eosinophilic airway inflammation (example 3). The specification also teaches increased expression of RUNX3 in an ovalbumin (OVA)-induced acute asthma mouse model developed by Topilski et al., 2002 (specification p 33-34. Figure 3.1). The specification further correlates the increased RUNX3 expression and increased pulmonary eosinophilia of the ova-treated mice to the increased pulmonary eosinophilia of RUNX3 knock out mice (specification p 33-34, example 4). The specification contemplates that up regulation of RUNX3 expression by an agent in the mature DCs in a subject in need thereof, will lead to reducing the proportion of mature DCs vs the immature DCs in said subject, thereby inhibiting inflammation (specification p, 5, lines 1-4). However, **(a)** the specification fails to correlate the OVA-induced increase in the RUNX3 expression in the bronchoalveolar lavage macrophages of mice to treating a T-cell mediated inflammation disorder in a subject having low activity or no activity of RUNX3 by delivering an active agent encoding RUNX3, thereby inhibiting the proliferation of T-cells; **(b)** the specification fails to provide any teachings with regard to attenuating dendritic cell (DC) maturation in a subject having low activity or no activity of RUNX3 transcription factor gene product, the method comprising delivering an active agent encoding RUNX3 that induces expression or over-expression of RUNX3 to the dendritic cells of said subject, thereby attenuating the dendritic cells maturation in a subject. Thus, as enablement requires the specification to teach how to make

and use the claimed invention, the specification fails to enable the claimed methods for treating a T-cell mediated inflammation or attenuating dendritic cell maturation in vivo byway of the claimed methods. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

As a first issue, the claims are directed to delivering an active agent encoding RUNX3 in vivo that induces expression or over-expression of RUNX3 in the immune cells thereby inhibiting the proliferation of T-cells resulting in the treatment of a T-cell mediated inflammation. The specification teaches increased RUNX3 expression in the pulmonary macrophages of an ova-induced acute asthma mouse model (specification p 33-34, Figure 3.1). However, the specification has failed to correlate the increased RUNX3 expression in the ova-challenged mice to the delivery of RUNX3 polynucleotide by any route of administration in vivo that induces overexpression of RUNX3 to the immune cells, inhibiting the proliferation of T-cells resulting in the treatment of a T-cell mediated inflammation. The specification also teaches perturbed distribution of CD4+/CD8+ T lymphocytes, increased ratio of mature to immature dendritic cells, increased levels of IL-5 and development of asthma-like symptoms in the RUNX3 knock out mice. However, the specification has failed to correlate the perturbed distribution of T cels in RUNX3 knock out mice to the delivery of RUNX23 polynucleotide in wild type mice where overexpression of RUNX3 in the immune cells of the wild type mice will inhibit T cell proliferation and treat a T cell mediated inflammatory disorder.

The specification teaches that RUNX3 k/o mice develop perturbed distribution of CD4+/CD8+ T lymphocytes, increased ratio of mature to immature dendritic cells, increased levels of IL-5 and development of asthma-like symptoms. The specification fails to correlate the perturbed distribution of CD4+/CD8+ T lymphocytes and the increased IL-5 levels to contacting cells with a polynucleotide encoding RUNX3 in vivo, wherein increased expression of RUNX3

will mediate a T cell-mediated or IL-5 mediated inhibition of inflammation. IL-5 is involved in the Th1/Th2 pathway of inflammatory diseases up regulating antibody formation via B cells and eosinophils (**Kidd,** Alternative Medicine Review, 8(3): 223-246, 2003) (p 225, figure 1). In inflammatory diseases T cell proliferation or Th2 proliferation is associated with interferon gamma secreted by the Th1 cells, where interferon gamma inhibits proliferation of Th2 cells (**Kidd,** Alternative Medicine Review, 8(3): 223-246, 2003) (p 225, figure 1). The art also teaches that, distinct from IL-5, novel or cytokines such as IL-9, IL-11, IL-13 and IL-25, are likely important in an inflammatory disease in regulating the Th1/Th2 pathway involved in T cell proliferation (Kidd p 234, 2nd column, 3rd paragraph). The specification has not provided evidence to correlate the perturbed distribution of CD4+/CD8+ T lymphocytes and the increased IL-5 levels in the RUNX3 k/o mice to increased expression of RUNX3 by contacting cells with a polynucleotide encoding RUNX3 resulting in inhibition of T cell proliferation in a subject in need thereof. However, the specification failed to provide guidance to correlate the increased IL-5 levels and the perturbed distribution of CD4+/CD8+ T lymphocytes in the RUNX3 k/o mice to the Th1/Th2 cytokine inflammatory biology of other species, as for example humans. The art teaches that some of the most important variables in the Th1/Th2 cytokine biology of inflammatory diseases include the species being researched, whether studies are done in vivo or ex vivo (**Kidd,** p 226, 1st column, 2nd paragraph). **Walsh** (Current Pharmaceutical Design, 11: 3027-3038, 2005) reports that disappointing results with humanized anti-IL-5 mAbs casts doubts on the role of the eosinpophil in asthma (p 3030, 1st column, last paragraph) and eosinophils are important in pro-inflammatory cells in asthma pathogenesis rather than inflammatory cells. Thus, the specification has not taught how increased levels of IL-5 in the Runx3 k/o mice relate to T cell proliferation and increased eosinophilia and whether the introduction of RUNX3 in the k/o mice will result in the inhibition of inflammation by regulating eosinophilia thru the Th1/Th2

pathway. At the time of the instant invention asthma is largely a Th2-driven disease, but much of this story is incomplete (Kidd, p 234, 2nd column, last paragraph).

As a second issue, claim 13 is directed to the delivery of a RUNX3 polynucleotide that induced overexpression of RUNX3 in the dendritic cells of a subject thereby attenuating the dendritic cell maturation in a subject. The specification teaches increased ratio of mature to immature dendritic cells, in the RUNX3 k/o mice associated with asthma-like symptoms and inflammatory diseases. The specification contemplates that when Runx3 is lost, epidermal Langerhans cells (LC) are absent and RUNX3 k/o DCs display accelerated maturation due to lack of responsiveness to TGF-beta and over-responsiveness to maturation inducing stimuli (specification, p 18). However, the specification fails to provide guidance to correlate the increased ratio of mature dendritic to immature dendritic cells in the k/o mice to the delivery of RUNX3 polynucleotide in dendritic cells in a subject having low or no activity of RUNX3 resulting in the attenuation of maturation of the dendritic cells. For example, in pulmonary inflammatory diseases, the art teaches that a more detailed phenotypic analysis of dendritic cells in their role of inflammatory processes in the pathogenesis of pulmonary arterial hypertension (PAH) will have to be performed (**Lambrecht et al,** Eur Respir J, 29: 435-437, 2007) p 436, 2nd column, last paragraph). The lack of significant effects of systemic steroids in idiopathic PAH patients provides an argument against the role of DCs in PAH (**Lambrecht,** p 436, 2nd column, last paragraph). **Lambrecht et al,** reports that the most important question even in 2007 is what is the functional role of dendritic cells in PAH (p 436, 1st column, 2nd paragraph). **Wallet et al,** (Clinical Medicine & Research, 3(3): 166-178, 2005) reports that the molecular targets of TGF-beta mediated suppression in DCs remain ill defined and one such target appears to be the RUNX3 transcription factor (p 170, 1st column, 2nd paragraph). **Wallet et al,** (Clinical Medicine & Research, 3(3): 166-175, 2005) indicates that primarily a contrasting role of DCs has been

described as a function of maturation where immature DCs were largely considered to be non-inflammatory or tolerogenic, but mature dendritic cells were considered capable of eliciting a pro-inflammatory immune responses and although generally correct, this paradigm is now proving too simple (p 166, 1st column). This issue is further complicated by the identification of distinct subtypes of dendritic cells that exhibit different antigen-presenting cell effector functions (abstract).

With regard to delivering a polynucleotide encoding RUNX3 (RUNX3 gene therapy), in vivo, wherein increased RUNX3 expression will result in the treatment of a T-cell mediated inflammation disorder in a subject in need thereof as contemplated by the specification the state of the art for inhibiting T cell mediated inflammation by gene therapy is unpredictable. In general, with regard to the gene therapy, while progress has been made in recent years for gene transfer in vivo, vector targeting to desired tissues in vivo continuous to be a limitation as supported by numerous teachings in the art. Numerous factors complicate the gene delivery art, which would not have been shown to overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into tissues, etc), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRMA produced, the stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically on the vector being used and the protein being produced. While progress has been made in recent years for in vivo, gene transfer, vector targeting in vivo to desired organs continuous to be unpredictable and inefficient. **Zhou et al,** (Medicinal Research Reviews, 24(6): 748-761, 2004) even after the filing of the instant application indicates that gene therapy requires gene systems with less toxicity and immunity,

high efficiency in gene transfer and the therapeutic gene expression in the targeted cells or tissues at functional level in a controllable manner (p 748, last paragraph). Zhou also notes to date, however, the gene delivery systems, including non-viral and viral vectors have somewhat immunogen inducing the host immune responses in gene therapy, which is one of the challenges of gene therapy (p 749, 1st paragraph). Zhou teaches that despite considerable progress over the past decade in the generation of gene transfer systems with reduced immunogenic properties, the remaining immunogen of many gene therapy vectors is still the major hurdle preventing their application in clinical trials, because the host immune responses induced by immunogen of the vectors lead to low level and short term of transgene expression, inefficient re-administration of the same vectors and severe side-effects in clinical trials (p 752, last paragraph). Zhou teaches that mice injected either intraperitoneal, intravenous or subcutaneously with rAAV-OVA developed strong OVA-specific CTL response, however, mice injected intramuscularly with the same virus developed minimal CTL response (p 755, 2nd paragraph). The specification however, has not provided any specific guidance or teachings with regard to the other modes of cell targeting or modes of administering RUNX3 therapeutic gene encompassed by the claims. With regard to the contact between the cells and the polynucleotide encoding RUNX3 is performed ex vivo, the art teaches that the purity of DC produced in vitro is questionable, and cultures could contain DC in different stages of development or other unknown contaminant cell types (**O'Neil et al,** Journal of Leukocyte Biology, 75: 600-603, 2004) (p 602, 2nd column, last paragraph). DC produced from different starting cell populations, such as monocytes and BM or cord blood can vary in their functional capacity (p 602, 2nd column, last paragraph).

In light of the above, the state of the art is suggesting that RUNX3 gene therapy might be feasible in the future. The instant specification does not provide any relevant teachings,

specific guidance, or working examples for overcoming the limitations of RUNX3 gene therapy or ex vivo RUNX3 gene therapy raised by the state of the art. The specification does not provide guidance for targeting RUNX3 polynucleotide into dendritic cells in vivo in a subject with low or no activity of RUNX3 resulting in the attenuation of maturation of dendritic cells. Therefore, the skilled artisan would conclude that the state of art of RUNX3 gene therapy is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for inhibiting inflammation by RUNX gene therapy without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for inhibiting inflammation by RUNX3 gene therapy, RUNX3 gene therapy ex vivo, or dendritic cell RUNX3 gene therapy, the lack of direction or guidance provided by the specification for inhibiting inflammation by RUNX3 gene therapy, RUNX3 gene therapy ex vivo, or dendritic cell RUNX3 gene therapy, the unpredictable state of the art with respect to RUNX3 gene therapy, RUNX3 gene therapy ex vivo, or dendritic cell RUNX3 gene therapy, the undeveloped state of the art pertaining to the inhibition of inflammation by RUNX3 gene therapy, RUNX3 gene therapy ex vivo, or dendritic cell RUNX3 gene therapy, and the breadth of the claims directed to all inflammatory diseases, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants argue that the specification clearly shows that deficiency in RUNX3 as demonstrated in RUNX3 knock out mice causes asthma like symptoms (heavy breathing, accelerated heart rate, eosinophilic infiltration etc) and these mice were shown to develop perturbations of CD4+/CD8+ T lymphocytes in the thymus, spleen and peripheral blood T cells and RUNX 3 expression is upregulated during dendritic cell maturation.

These arguments re not persuasive because applicants have not provided guidance to

correlate the RUNX3 knock out mouse perturbed distribution of the T lymphocytes to the delivery of RUNX3 nucleotide in wild type animals by any route of administration where overexpression of RUNX3 inhibits proliferation of T lymphocytes or targeting dendritic cells thereby attenuating maturation of dendritic cells in a RUNX3 wild type subject. As discussed above RUNX3 gene therapy is unpredictable with regard to route of RUNX3 administration and targeting dendritic cells in vivo.

Applicants argue that most importantly the specification has provided a human study conducted on asthma patients demonstrating that particular SNPs in the RUNX3 gene were found to correlate with asthma in humans.

These arguments are not persuasive because the detection of SNPs in the asthma patients does not correlate to the RUN3 gene therapy by way of the claimed methods.

Applicants argue that it is improper for the patent office to request evidence regarding the degree of effectiveness of a compound in humans.

The MPEP only states the examiner cannot ask for clinical trial data regarding safety or efficacy for enablement. No such requirement is in the present record. The MPEP has not prohibition as to reviewing clinical trial data to determine enablement at the time of filing. No body of evidence is removed from consideration by the MPEP. Applicant's claims encompass a treatment with RUNX3 gene therapy or no effect. There is no enabled use for no effect. In the present situation, clinical trial data in conjunction with references all together establish at the time of filing the claimed methods and therapeutic methods lacked enablement as the skilled artisan would have needed to perform an undue amount of experimentation without a predictable degree of success to implement in the invention as claimed.

Applicants have argue as evidenced by the provided references prior to the filing date of the instant application, the art was replete with teachings for preparing gene delivery systems

and administering same with a reasonable expectation of success in transferring genetic information to treat inherited or acquired disorders.

These arguments are not persuasive because as discussed above RUNX3 gene therapy is unpredictable byway of the claimed methods. The references cited by the applicants are not enabling the claimed invention because do not address the issue of targeting the RUNX3 to immune cells in a subject where expression or overexpression of RUNX3 inhibits proliferation of T-cells resulting in the treatment of a T-cell mediated inflammation disorder. For example, Albelda et al, provides a review of vectors useful in gene therapy and concludes that while gene therapy is in its infancy, genes have been safely and successfully transferred into animals and patients. Kay for example discuses gene transfer and expression of factor IX in haemophilia B patients treated with an AAV vector. However, the issue is not the safety nor the vectors to successfully transfer genes into animals but as to whether the RUNX3 nucleic acid will target the immune cells in vivo and as to whether the RUNX3 nucleic acid will be expressed at sufficient levels within the immune cells to inhibit T cell proliferation with an effect on a T cell mediated disorder. The art teaches that transgene expression in vivo is depending upon the route of administration of a nucleic acid and the dose of a nucleic in vivo. In pursuing gene therapy, it is important to induce transgene expression for a long time in a tissue specific manner in the instant case in immune cells without strong immune responses against vectors, transgene products, and transduced cells.

Applicants argue that the RUNX3 peptide was known to those of ordinary skill in the art at the time of filing and was therefore available as of the date of invention.

These arguments are not persuasive because the issue is not the availability of the RUNX3 peptide but the issue is the unpredictability of RUNX3 gene therapy as discussed above.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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